

Original Article

Incidental prostate cancer diagnosed at radical cystoprostatectomy for bladder cancer: disease-specific outcomes and survival



Joshua B. Kaelberer^a, Michael A. O'Donnell^b, Darrion L. Mitchell^a, Anthony N. Snow^c, Sarah L. Mott^d, John M. Buatti^a, Mark C. Smith^a, John M. Watkins^{a,*}

^a Department of Radiation Oncology, University of Iowa, Carver College of Medicine, Iowa City, IA, USA

^b Department of Urology, University of Iowa, Carver College of Medicine, Iowa City, IA, USA

^c Department of Pathology, University of Iowa, Carver College of Medicine, Iowa City, IA, USA

^d Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA, USA

ARTICLE INFO

Article history:

Received 18 May 2016

Received in revised form

15 June 2016

Accepted 16 June 2016

Available online 23 June 2016

Keywords:

Bladder neoplasms

Cystoprostatectomy

Prostate neoplasms

ABSTRACT

Background: The current standard of care for men with muscle-invasive bladder cancer is radical cystoprostatectomy (RCP). One-third of RCP specimens demonstrate incidental prostate cancer, primarily reported in small series with limited follow-up. The aim of this study is to report mature outcomes, including patterns of failure and disease-specific recurrence rates, and survival, for a large cohort of men with incidental prostate cancer at RCP performed at a tertiary referral center.

Methods: This retrospective study describes cancer control and survival rates for men who underwent RCP for bladder cancer and were found incidentally to have prostate cancer. Analysis of patient-, tumor-, and treatment-specific factors were analyzed for association with disease control and survival endpoints.

Results: Between 2002 and 2010, 94 patients with incidental discovery of prostate cancer postRCP were identified for inclusion in this study. Forty-five patients (45%) underwent RCP for recurrent (rather than initial presentation of) bladder carcinoma. At a median follow-up of 40.3 months (71.2 months for survivors; range, 8.9–155.5 months), 42 patients were alive without recurrence and 52 patients had died (25 associated with disease). The estimated 5-year bladder cancer disease-free, urinary tract malignancy disease-free, and prostate specific antigen (PSA) relapse-free survivals were 76% [95% confidence interval (CI), 65–84%], 64% (52–74%), and 97% (79–100%), respectively. The estimated 5-year urinary tract malignancy-specific and overall survivals were 61% (49–71%) and 52% (41–62%), respectively. Univariate analysis demonstrated associations between pathologic T/N-stage and nodal ratio with bladder cancer disease-free, urinary tract malignancy disease-specific, and overall survivals, with patient age at diagnosis as an additional adverse factor associated with overall survival. Multivariate analysis confirmed pN-stage and age as independently associated with worse survival.

Conclusion: For men undergoing RCP for bladder cancer, the present study suggests that incidentally discovered prostate cancers, irrespective of pathologic stage, Gleason score, or clinical significance, do not impact 5-year disease control or survival outcomes.

Copyright © 2016 Asian Pacific Prostate Society, Published by Elsevier. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Radical cystoprostatectomy (RCP) is currently a standard-of-care curative-intent management option for patients with muscle-invasive and/or multiply recurrent urothelial carcinoma of the bladder.¹ With 5-year survival rates of ~50%, the identification of

incidental prostate cancer within the RCP specimen rarely impacts management considerations.² Several single-institution series have focused on reporting the general incidence and rates of “clinically significant” incidental prostate cancers in RCP specimens, with variable quality and duration of follow-up;² however, few series have reported on long-term disease-specific survival and patterns of failure, following resection of both pathologic processes.^{2,3} The present investigation seeks to describe disease control and survival outcomes for patients incidentally diagnosed with prostate cancer

* Corresponding author. Department of Radiation Oncology, Carver College of Medicine, University of Iowa, 200 Hawkins Drive, Iowa City, Iowa, 52242, IA, USA.

E-mail address: john.m.watkins.md@hotmail.com (J.M. Watkins).

at the time of RCP for bladder cancer, performed at a high-volume academic tertiary referral center.

2. Materials and methods

This retrospective study was approved by the Institutional Review Board at the participating institution (University of Iowa Hospitals and Clinics). Patients eligible for the study were identified from a query of electronic medical records, selecting for patients diagnosed with prostate cancers at the time of RCP. Patients with known diagnosis of prostate cancer prior to RCP or RCP performed for reasons other than bladder cancer were excluded from the study, as were patients with clinically or radiographically evident metastatic disease prior to RCP. Patients with insufficient follow-up (nonmortality early loss to follow-up < 3 months postRCP) were also excluded. Data were collected from existing databases and electronic medical records. Data fields included patient demographics, staging characteristics (for bladder cancer), as well as tumor and treatment specific variables. Additionally, timing and patterns of disease failure (specific to the type of recurrent disease) were recorded, as were disease status and survival at previous follow-up.

Pathologic assessment of the cystoprostatectomy specimen involved external examination of the specimen, including orientation and identification of the distal ureters, as well as specimen size and weight recording. Of note, urethral and distal urethral margins are frequently removed before receipt of the specimen for intraoperative assessment of these margins. The external surface is examined for gross involvement by tumor and differentially inked for orientation (i.e., left/right). The specimen is then inflated with and submerged in 10% buffered formalin and allowed to fix overnight. If the specimen is not amenable to inflation (due to disruption or other irregularity), it may be opened anteriorly, taking care to avoid the primary tumor location upon opening, and padded with gauze before formalin fixation, to ensure preservation of the gross architecture. After fixation, standard sections are taken to assess margins and staging. Pertinent sections taken for microscopic evaluation include representative sections of tumor foci including the area of deepest invasion, the closest approach to the deep margin, and any other margins closely approximated by the tumor. The relationship with the trigone, ureters, and prostate are also documented and sampled. Representative sections from grossly uninvolved areas are taken. The ureters are opened longitudinally to grossly evaluate for the presence of a tumor. After any pertinent sections are taken to evaluate the relationship the bladder and/or tumor to the prostate, the prostate is serially sectioned in a plane perpendicular to the prostatic urethra. Grossly identified lesions are sampled. If no lesions are noted grossly, representative transverse sections are submitted entirely to represent ~50% of the prostatic tissue including the bases of the seminal vesicles and the proximal ends of the vasa deferentia. The distal urethra is submitted entirely by removing it in a cone-shape and radially sectioning it. Any lymph nodes identified in associated adipose tissue are submitted entirely.

“Clinically significant” prostate cancers were defined using established histopathologic factors,² including any one of the following: pathologic Gleason score > 6, pelvic lymph node involvement, invasion of the seminal vesicle(s), or positive surgical margin(s).

All patients in the study were subject to standard follow-up procedures. This included urologic oncologist follow-up with urine cytology and computed tomography (CT) imaging every 3–6 months for 2 years postRCP, then annual follow up with cytology and imaging upon suspicion. With regard to prostate cancer surveillance, serum prostate specific antigen (PSA) was followed at the

discretion of the managing urologic oncologist, and/or as coordinated with the patient's local urologist or primary care physician.

The outcome variables measured in this study included overall survival (OS), as well as disease-free survival (DFS) and disease specific survival (DSS), specific to each: bladder cancer, genitourinary (GU) tract malignancy, and prostate cancer. Relationships between patient-, tumor-, and treatment-specific factors were analyzed for statistically significant associations with these endpoints. OS was measured from date of RCP to previous follow-up or death. DFS was measured from the date of RCP to the earliest sign of clinical or radiographic disease recurrence, previous urologic oncology follow-up, or death, with recurrence and treatment-associated death scored as events. Specific to prostate cancer DFS (i.e., PSA relapse-free survival), patients who had a PSA elevation to ≤ 0.1 were not scored as events. Additionally, PSA relapse-free survival estimates employed only interval to most recently recorded PSA value. DSS was measured from date of RCP to previous follow-up or death, with death at time of active disease or from cancer-specific intervention scored as events. Patients without evidence of recurrence within 3 months of death were classified as “died of other cause,” and not scored as events for DFS or DSS, with interval calculated at death. Patients known to have died but who had been lost to follow-up for > 3 months were classified as “died of indeterminate cause,” and were not scored as events for DFS or DSS, with interval calculated at previous urologic oncology clinical evaluation.

2.1. Statistical analysis

Survival probabilities were estimated and plotted using the Kaplan–Meier method. Estimates along with 95% pointwise confidence intervals were reported. Univariate and multivariate Cox proportional hazards regression was used to assess the effects of the clinicopathologic variables on the outcomes of interest. The use of a stepwise selection procedure, variables significantly associated with each outcome at the univariate level and having < 10% missing information were considered for inclusion in the multivariate model. All statistical testing was two-sided and assessed for significance at the 5% level using SAS, version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

Between 2002 and 2010, 307 patients underwent RCP for bladder cancer, of whom 103 had prostate cancers identified (33.6%). Ninety-four patients met criteria and were included in the present investigation. Reasons for exclusion were: prostate cancer diagnosis known prior to RCP ($n = 7$), RCP performed for nonbladder-cancer etiology ($n = 5$), metastases identified prior to RCP ($n = 5$), and postRCP follow-up < 3 months and lost to follow-up ($n = 4$). Median age was 70 years old (range, 41–85), and 98% of patients were white ($n = 92$). Approximately half (45%; $n = 42$) of patients had history of prior urothelial carcinoma at the time of presentation for RCP, including 20 of 27 patients without preRCP evidence of muscle-invasive disease. The majority of patients (71%; $n = 67$) had pathologic or radiographic demonstration of muscle-invasive or more advanced disease (> cT2 and/or N+). Per study design, no patient was known to have diagnosis of prostate cancer at time of RCP. Additional demographic and preRCP tumor, staging, and work-up characteristics are outlined in Table 1.

For RCP, all but two patients underwent open RCP, with the remaining two performed laparoscopically (without robot assistance). Pathologic details are demonstrated in Table 2. Of note, nine patients had undergone preoperative (neoadjuvant) chemotherapy (10%), and 11 patients received postoperative (adjuvant)

chemotherapy (12%). No patient underwent pre- or postoperative radiation therapy.

For the overall population, at a median follow-up of 40.3 months (71.2 months for survivors; range, 8.9–155.5 months, with 74% followed ≥ 5 years and 21% followed ≥ 8 years), there were a total of 42 surviving patients (38 without recurrence and 4 recurrent GU malignancies, all salvaged and without active disease) and 52 had died (22 with recurrent GU malignancy, 3 from complications of cancer-directed therapy, 10 of nonGU malignancy cause, and 17 of indeterminate etiology). For the three patients who died of cancer-directed therapy, one each experienced fatal postoperative pulmonary embolism, postoperative aspiration pneumonia, and retroperitoneal hemorrhage following dilation of nonmalignant uretero-ileal anastomotic stricture (36 months postRCP). For patients who died of nonGU malignancy etiology, reasons included: stroke ($n = 1$), hepatocellular carcinoma ($n = 1$), nonsmall-cell lung cancer ($n = 1$), glioblastoma multiforme ($n = 1$), idiopathic pulmonary fibrosis ($n = 1$), end-stage renal failure ($n = 1$), and unknown cause but without disease within 3 months of death ($n = 4$). The estimated 5-year overall survival for the entire population was 52% [95% confidence interval (CI), 41–62%; Fig. 1].

Specific to GU tract malignancies, 29 patients experienced disease recurrence, including 19 felt to be true recurrence of bladder

cancer, another nine new GU tract primary tumors, and one indeterminate (lost to clinical follow-up, records report “metastatic bladder cancer” as cause of death). Six of these patients were successfully salvaged, primarily with resection ($n = 3$), intraureteral therapy ($n = 2$), or both ($n = 1$). All but two of these patients remain alive, without evidence of disease, with the remaining patients dying of unknown cause (without clinical or radiographic evidence of active disease at follow-up 3 months and 6.5 months prior to death, respectively). An additional patient was known to have disease recurrence, with salvage treatment elsewhere, having later died of indeterminate cause (scored as “died unknown cause,” owing to 15-month lapse between previous record and death). Patterns of GU disease failure are demonstrated in Table 3.

The estimated 5-year DFS for bladder and GU tract cancers were 76% (65–84%; Fig. 2) and 64% (52–74%; Fig. 3), respectively. The estimated GU tract malignancy DSS was 61% (49–71%; Fig. 4).

Univariate analysis of factors associated with GU tract malignancy DFS demonstrated statistically significant association with recurrent disease at the time of RCP (vs. initial presentation of bladder pathology; Table 4). Univariate analysis of factors associated with GU tract malignancy DSS demonstrated statistically significant associations with pathologic T- and N-stage; upon multivariate analysis, only pathologic N-stage was independently associated with GU tract malignancy-specific mortality.

Specific to prostate cancer, the majority of patients had Gleason < 6 with negative surgical margins ($n = 61$; 65%). Additional pathologic data are characterized in Table 5. Of note, 31 patients (33%) had characteristics of “clinically significant” tumors, including seven with positive margin (all but 2 patients of which were Gleason > 6). No patient had seminal vesicle

Table 1
Patient demographic and preoperative tumor, staging, and work-up data.

Variable	RCP ($n = 94$)	
		N (%)
Age		
Median	70	
(Range)	(41–85)	
≥ 75 y		29 (31)
Race		
Caucasian		92 (98)
Prior urothelial cancer?		42 (45)
Median times recurrent	2	
(Range)	(1–8)	
Bladder clinical stage		
cTis/Ta (0)		8 (9)
cT1N0 (I)		19 (20)
cT2N0 (II)		59 (63)
cT3N0 (III)		2 (2)
cT4aN0 (III)		3 (3)
cN+ (IV)		3 (3)
Pelvis staging studies		
CT		87 (93)
MRI		4 (4)
PET		2 (2)
None		2 (2)
Thoracic staging studies		
Chest X-ray		77 (82)
Chest CT		15 (16)
PET		0 (0)
None		2 (2)
Osseous staging		
Bone scan		27 (29)
PET		2 (2)
Bone scan + PET		1 (1)
None		64 (68)
PSA		
Performed < 1 y preRCP		25 (27)
Median	2.0 ng/mL	
(Range)	(0.2–8.6)	
> 4.0		7 (7)

Note. Data in the “Bladder clinical stage” section as per “AJCC Cancer Staging Manual,” by Edge, S., et al, 2010, 7th Edition. Copyright 2011, Springer Science+Business Media, LLC.

CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; PSA, prostate specific antigen; RCP, radical cystoprostatectomy.

Table 2
Bladder cancer-specific pathologic data.

Variable	RCP ($n = 94$)	
		N (%)
Interval biopsy to RCP ^{a)}		
Median interval	48 d	
(Range)	(7–224)	
> 100 d		3 (3)
Specimen volume		
Median	390 g	
(Range)	(230–1,850)	
Pathologic T-stage ^{a)}		
pTa		2 (2)
pTis		3 (4)
pT1		9 (11)
pT2		28 (33)
pT3		33 (39)
pT4		9 (11)
Pathologic N-stage ^{a)}		
pN0		62 (73)
pN1		9 (11)
pN2		11 (13)
pN3		3 (4)
Pathology findings		
Perineural invasion ^{b)}		28 (35)
Lymphovascular invasion ^{b)}		42 (51)
Involved margin(s)		9 (10)
Involved LN(s)		42 (51)

^{a)} Excludes nine patients who underwent preoperative chemotherapy; staging as per “AJCC Cancer Staging Manual,” by Edge, S., et al, 2010, 7th Edition, Copyright 2011, Springer Science+Business Media, LLC. One patient each experienced biopsy to RCP interval > 100 days for: intravesicle gemcitabine/mitomycin C toxicity (224 days), intravesicle BCG-associated toxicity (126 days), and patient-associated scheduling delay (102 days).

^{b)} Excludes 14 patients and 11 patients without recorded perineural and lymphovascular invasion data, respectively.
LN, lymph nodes; RCP, radical cystoprostatectomy.

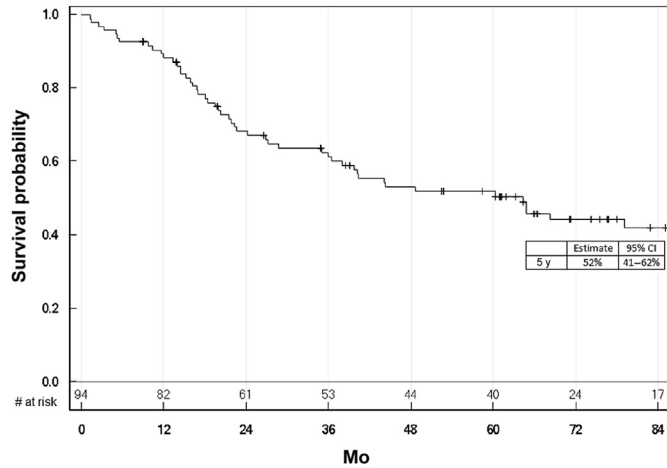


Fig. 1. Overall survival for the study population.

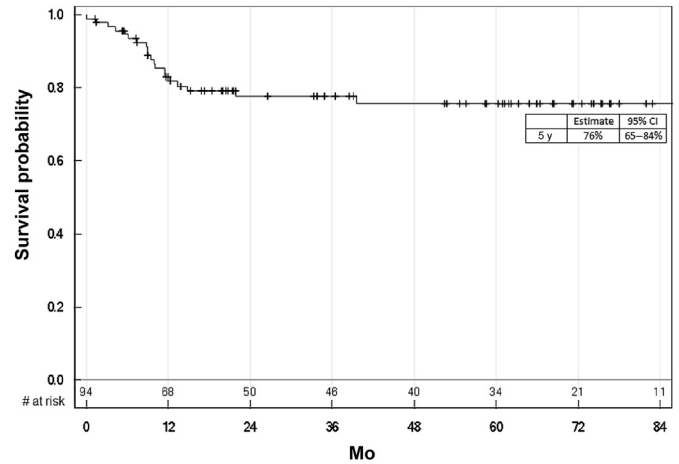


Fig. 2. Bladder cancer-specific disease-free survival.

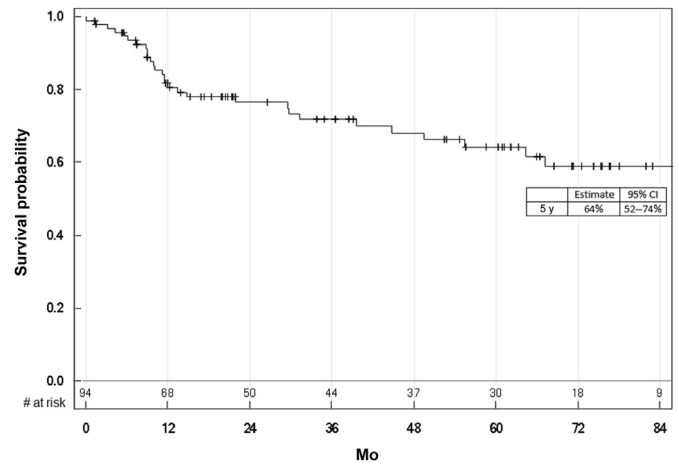


Fig. 3. Urinary tract malignancy-specific disease-free survival.

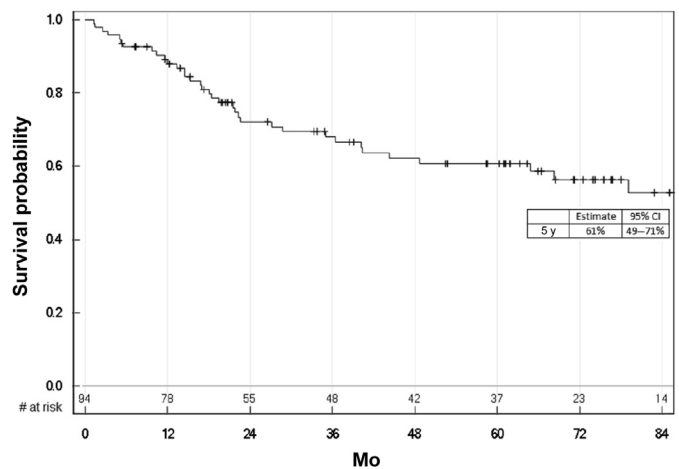


Fig. 4. Urinary tract malignancy disease-specific survival.

invasion or lymph node involvement. Fifty-eight patients (62%) had initial surveillance PSA performed within 1 year postRCP, all of which were ≤ 0.05 ng/mL. At a median PSA follow-up of 29.8 months (3.0–147.2, with 29% at ≥ 5 years), only one patient had experienced PSA relapse, involving an initial rise to 0.30 at 44.7 months postRCP, with very gradual subsequent rise to 0.41 (PSA doubling time 183.5 months; no intervention performed). It is noteworthy that this patient did not have any “clinically significant” pathologic features (pT2aN0, Gleason 3 + 3 = 6, without extraprostatic extension, seminal vesicle invasion, or positive margin). Additionally, six patients had minimal detectable postRCP PSA elevation to ≤ 0.1 , were followed without intervention, and were thus not scored as PSA relapses. The estimated 5-year PSA relapse-free survival for the population was 97% (79–100%; Fig. 5). No patient experienced symptomatic recurrence of prostate cancer, nor did any undergo salvage intervention for PSA rise or recurrence.

4. Discussion

In many industrialized nations, including the United States, prostate cancer is the most common cancer in males.¹ Although the value of physical examination and serologic screening methods for prostate cancer remains controversial,⁴ the fact remains that many men diagnosed with clinically localized disease will die with, rather than of, prostate cancer, irrespective of intervention.⁵ Autopsy series have confirmed high rates of incidental prostate cancers, with the majority of men having survived without formal diagnosis of malignancy.⁶ Specific to patients undergoing RCP, the reported rates of incidental prostate cancers are 14–50%,^{3,7–11} which aligns well with our own experience (34%). Likely, differences in pathologic processing technique play a role in the variable reported

Table 3

Patterns of genitourinary tract malignancy failure for patients with radical cystoprostatectomy performed for bladder cancer, with incidental prostate cancer identified in pathologic specimen.

	n (%) ^{a)}
Local only	1 (1)
Regional nodal only	1 (1)
Locoregional + distant	3 (3)
Distant only	14 (15)
Nonbladder GU tract	9 (10)
Unknown	1 (1)

^{a)} Denominator excludes three patients with treatment-associated mortality. GU, genitourinary.

incidence, with more meticulous sampling (e.g., 2–3 mm step-sectioning of whole-mount specimen) responsible for increased detection.¹² This is further suggested by higher relative rates of “clinically insignificant” disease in series with higher detection rates.^{3,7} There does remain some debate concerning the high

Table 4

Univariate analyses of variable association with genitourinary tract malignancy-specific disease-free survival (DFS) and disease-specific survival (DSS).

	DFS		DSS	
	HR (95% CI)	P	HR (95% CI)	P
Age (units = 1)	1.02 (0.98–1.06)	0.38	1.03 (0.99–1.06)	0.16
Interval biopsy to surgery (units = 1)	1.01 (0.99–1.02)	0.39	0.99 (0.98–1.01)	0.41
Prior urothelial cancer	2.16 (1.02–4.58)	0.04	1.32 (0.68–2.55)	0.42
Clinical stage	0.63 (0.30–1.31)	0.21	1.17 (0.56–2.44)	0.68
Preoperative chemotherapy	1.17 (0.35–3.89)	0.79	1.08 (0.38–3.09)	0.89
Bladder pT-stage ^{a)}	1.50 (0.69–3.25)	0.30	2.44 (1.17–5.12)	0.02
Bladder pN-stage ^{a)}	1.87 (0.80–4.37)	0.15	3.11 (1.51–6.43)	< 0.01
Nodal ratio ^{a)}	1.04 (0.28–3.91)	0.95	1.32 (0.45–3.86)	0.61
Bladder margin	0.77 (0.18–3.27)	0.73	1.05 (0.32–3.43)	0.94
Bladder perineural invasion	1.11 (0.49–2.51)	0.81	0.85 (0.40–1.79)	0.66
Postoperative chemotherapy	0.89 (0.27–2.96)	0.85	1.08 (0.38–3.09)	0.88

Note. Data in the “clinical stage”, “Bladder pT-stage”, and “Bladder pN-stage”, sections as per “AJCC Cancer Staging Manual,” by Edge, S., et al, 2010, 7th Edition. Copyright 2011, Springer Science+Business Media, LLC.

Statistically significant findings identified in bolded font.

^{a)} For purposes of univariate analysis, clinical stage dichotomized to 0–I versus II–IV, bladder pT stage dichotomized to 0–2 versus 3–4, bladder N-stage dichotomized to 0 versus 1–3, and nodal ratio to $\geq 20\%$ versus $< 20\%$ (with only N+ patients included).

CI, confidence interval; HR, hazard ratio (for dichotomized data).

coincidence of these tumors, specific to a common carcinogenic pathway;² however, this remains speculative, and further investigation is required. Investigators from the Polytechnic University of the Marche Region in Italy suggest incidental prostate cancers are biologically less aggressive.^{8,13} Whether this is inherent to a population of patients with synchronous bladder cancer or merely an early representation of the natural history of prostate cancer remains to be determined.

Within the literature specific to incidentally-identified prostate cancers, the term “clinically significant” has been routinely applied, employing factors such as: seminal vesicle invasion, positive surgical margins, pathologic Gleason Score > 6 , pelvic lymph node involvement, or tumor volume > 0.5 cc.² Prior series of incidental prostate cancers identified at RCP have described low rates of biochemical relapse ($< 5\%$) and prostate-cancer specific mortality (0%), irrespective of this terminology.^{3,9–11} Specific to our population, 31 patients had “clinically significant” pathologic features, none of whom experienced PSA failure. As only one patient had very gradual PSA rise unlikely to be associated with prostate cancer-specific mortality (PSA doubling time of 183 months),¹⁴ and no patient experienced symptomatic recurrence of prostate cancer, use of the term “clinically significant” would seem inaccurate, at least with respect to prostate cancers diagnosed incidentally at RCP for muscle-invasive bladder cancer. It is noteworthy that we did not report on volume of prostate carcinoma (with < 0.5 cc vs. > 0.5 cc as determinant), as this data point was not prospectively recorded.

In terms of prostate cancer surveillance in this setting, as the bladder cancer diagnosis warranting RCP demonstrates the more aggressive pathologic process, it would seem prudent to perform initial postRCP PSA within 1–3 months postoperatively, following annually thereafter, in the absence of highly aggressive features

Table 5

Prostate cancer-specific pathologic data.

Variable	N (%)
Gleason score at RCP	
4	3 (3)
5	4 (4)
6	58 (62)
7	28 (30)
8	0 (0)
9	1 (1)
Pathologic T-stage	
pT2a	46 (49)
pT2b	5 (5)
pT2c	40 (43)
pT3a	3 (3)
Pathology findings	
Perineural invasion ^{b)}	28 (35)
Lymphovascular invasion ^{b)}	42 (51)
Extraprostatic extension	5 (5)
Involved seminal vesicle(s)	0 (0)
Involved margin(s)	7 (7)
Involved LN(s)	0 (0)
Clinically Significant ^{c)}	31 (33)

Note. Data in the “clinical stage”, “Bladder pT-stage”, and “Bladder pN-stage”, sections as per “AJCC Cancer Staging Manual,” by Edge, S., et al, 2010, 7th Edition. Copyright 2011, Springer Science+Business Media, LLC.

^{a)} Delayed RCP due to preoperative chemotherapy.

^{b)} Excludes 13 and 24 patients without recorded perineural and lymphovascular invasion data, respectively.

^{c)} Defined as seminal vesicle invasion, positive surgical margins, pathologic Gleason Score > 6 , or pelvic lymph node involvement.

LN, lymph node(s); RCP, radical cystoprostatectomy.

(e.g., Gleason 8–10, pelvic nodal or seminal vesicle involvement, multifocal or large extent of positive margin).² Adjuvant hormone or radiation therapy does not appear warranted in this setting, specific to the prostate cancer diagnosis.

Specific to bladder cancer, the 5-year disease control and survival rates for the present series compare well with prior incidental prostate cancer series³ as well as those of trial participants.¹⁵ This would suggest that bladder carcinoma in the setting of concomitant prostate cancer does not behave more aggressively, and is most likely to be coincidental rather than correlated. Although one small series demonstrated poorer outcome for postRCP bladder cancer patients with incidental prostate cancers (as compared with those without prostate cancer),¹⁶ our data, constituting the second largest report to date, do not appear to support this. Similarly, in the largest published series on this topic, investigators at the University of Southern California did not demonstrate differences in survival between RCP-managed bladder cancer patients with and without incidental prostate adenocarcinoma.³ In this series, which included 1,476 patients who underwent RCP between 1970 and 2008 for urothelial carcinoma of the bladder (without prior known history of prostate cancer), 559 patients (38%) were identified to have incidental prostate adenocarcinoma ($n = 123$ “clinically significant”). Of note, prostatic stromal invasion by urothelial carcinoma was significantly associated with worse 10-year overall survival (22%) than superficial prostatic urethral/duct (43%) or no prostatic involvement (47%).

A weakness of the present investigation is the limited data on bladder cancer disease-specific survival, primarily owing to 17 patients whose death occurred > 3 months from their previous recurrence-free clinical follow-up. Although unfortunate, this was anticipated, primarily owing to patients’ long-distance travel to our tertiary referral center. As such, patients were frequently referred back to their local community urologist after 3–5 years of follow-up, or sooner upon patient preference, with variable continued correspondence.

Within the present investigation, the predominant patterns of failure were distant recurrences and new GU tract primaries (28 of

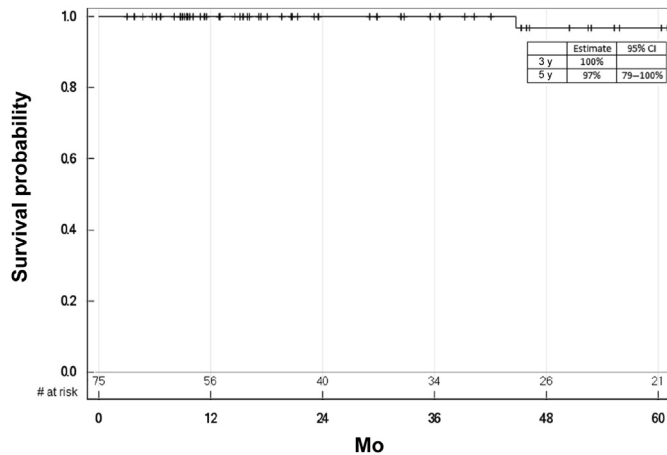


Fig. 5. PSA relapse-free survival. PSA = prostate specific antigen.

30 recurrences with documented failure site), with only two locoregional-only failures. This is similar to prior series on this topic,³ and muscle-invasive bladder cancer generally.¹ Given the low utilization of pre- and postoperative chemotherapy in our series, the distant pattern of failure would suggest potential for improvement. Randomized trials of pre- and postoperative chemotherapy have demonstrated improved cancer control and survival for bladder cancer patients who undergo RCP for bladder cancer.^{13,17–19} Whether this effect is preserved in patients with synchronous prostate cancers remains to be determined. With respect to locoregional control, Although limited data suggest an opportunity for pelvis-directed radiotherapy to improve pelvic disease control (particularly in the setting of involved margins),²⁰ the infrequency of such failures in our study population limits our ability to comment further.

Our investigation identified statistically significant associations between lymph node ratio and GU tract-specific and overall survivals. Given the distant pattern of failure, it appears that increasing nodal burden reflects a higher probability of occult metastatic disease, as this factor has been previously reported as independently associated with disease control and survival.²¹ Whether patients may experience differential benefit of adjuvant chemotherapy when specifically stratified by nodal ratio remains to be determined.

5. Conclusion

Incidental prostate cancer identified at RCP for urothelial bladder cancer appears to have little impact on the natural history of disease, with GU tract malignancy-related recurrence and mortality dominating as the most common pattern. In long-term bladder cancer survivors, the intermediate-term PSA relapse rate appears to be very low, irrespective of “clinically significant” features.

Conflicts of interest

The authors have no conflicts of interest or financial ties to disclose.

References

- Kaufman D, Shipley W, Feldman A. Bladder cancer. *Lancet* 2009;374:239–49.
- Damiano R, Di Lorenzo G, Cantiello F, De Sio M, Perdoni S, D'Armiento M, et al. Clinicopathologic features of prostate adenocarcinoma incidentally discovered at the time of radical cystectomy: an evidence-based analysis. *Eur Urol* 2007;52:648–57.
- Bruins HM, Djaladat H, Ahmadi H, Sherrod A, Cai J, Miranda G, et al. Incidental prostate cancer in patients with bladder urothelial carcinoma: comprehensive analysis of 1,476 radical cystoprostatectomy specimens. *J Urol* 2013;190:1704–9.
- Carlsson S, Vickers AJ, Roobol M, Eastham J, Scardino P, Lilja H, et al. Prostate cancer screening: facts, statistics, and interpretation in response to the US Preventive Services Task Force review. *J Clin Oncol* 2012;30:2581–4.
- Albertsen PC, Moore DF, Shih W, Lin Y, Li H, Lu-Yao GL. Impact of comorbidity on survival among men with localized prostate cancer. *J Clin Oncol* 2011;29:1335–41.
- Yin M, Bastacky S, Chandran U, Becich MJ, Dhir R. Prevalence of incidental prostate cancer in the general population: a study of healthy organ donors. *J Urol* 2008;179:892–5.
- Mazzucchelli R, Barbisan F, Scarpelli M, Lopez-Beltran A, van der Kwast TH, Cheng L, et al. Is incidentally detected prostate cancer in patients undergoing radical cystoprostatectomy clinically significant? *Am J Clin Pathol* 2009;131:279–83.
- Montironi R, Mazzucchelli R, Santinelli A, Scarpelli M, Beltran AL, Bostwick DG. Incidentally detected prostate cancer in cystoprostatectomies: pathological and morphometric comparison with clinically detected cancer in totally embedded specimens. *Hum Pathol* 2005;36:646–54.
- Moutzouris G, Barbatis C, Plastiras D, Mertziotis N, Katsifotis C, Presvelos V, et al. Incidence and histological findings of unsuspected prostatic adenocarcinoma in radical prostatectomy for transitional cell carcinoma of the bladder. *Scand J Urol Nephrol* 1999;33:27–30.
- Aytac B, Vuruskan H. Clinicopathologic features of incidental prostatic adenocarcinoma in radical cystoprostatectomy specimens. *World J Surg Oncol* 2011;9:81.
- Delongchamps NB, Mao K, Theng H, Zerbib M, Debre B, Peyromaure M. Outcome of patients with fortuitous prostate cancer after radical cystoprostatectomy for bladder cancer. *Eur Urol* 2005;48:946–50.
- Desai A, Wu H, Sun L, Sesterhenn IA, Mostofi FK, McLeod D, et al. Complete embedding and close step-sectioning of radical prostatectomy specimens both increase detection of extra-prostatic extension, and correlate with increased disease-free survival by stage of prostate cancer patients. *Prost Cancer Prost Dis* 2005;5:212–8.
- Montironi R, Mazzucchelli R, Barbisan F, Stramazotti D, Santinelli A, Scarpelli M, et al. HER2 expression and gene amplification in pT2a Gleason score prostate cancer incidentally detected in cystoprostatectomies: comparison with clinically detected androgen-dependent and androgen-independent cancer. *Hum Pathol* 2006;37:1137–44.
- D'Amico AV, Chen MH, Roehl KA, Catalona WJ. Identifying patients at risk for significant versus clinically insignificant postoperative prostate-specific antigen failure. *J Clin Oncol* 2005;23:4975–9.
- Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. *N Engl J Med* 2003;349:859–66.
- Skinner DG, Daniels JR, Russell CA, Lieskovsky G, Boyd SD, Nichols P, et al. The role of adjuvant chemotherapy following cystectomy for invasive bladder cancer: a prospective comparative trial. *J Urol* 1991;145:459–64.
- Sruogis A, Ulys A, Smailyte G, Kardelis Z, Kulboka A, Anglickiene G, et al. Incidentally found prostate cancer and influence on overall survival after radical cystoprostatectomy. *Prostate Cancer* 2012;2012:690210.
- Stöckle M, Meyenburg W, Wellek S, Voges G, Gertenbach U, Thuroff JW, et al. Advanced bladder cancer (stages pT3b, pT4a, pN1 and pN2): improved survival after radical cystectomy and three adjuvant cycles of chemotherapy. Results of a controlled prospective study. *J Urol* 1992;148:302–6.
- Ruggeri EM, Giannarelli D, Bria E, Carlini P, Felici A, Nelli F, et al. Adjuvant chemotherapy in muscle-invasive bladder cancer: a pooled analysis from phase III studies. *Cancer* 2006;106:783–8.
- Baumann BC, Guzzo TJ, He J, Vaughn DJ, Keefe SM, Vapiwala N, et al. Bladder cancer patterns of pelvic failure: implications for adjuvant radiation therapy. *Int J Radiat Oncol Biol Phys* 2013;85:363–9.
- Herr HW. Superiority of ratio based lymph node staging for bladder cancer. *J Urol* 2003;169:943–5.